

Fesoterodine Fumarate Extended-Release (Toviaz™—Pfizer Labs)
AHFS 86:12 Genitourinary Smooth Muscle Relaxants

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Executive Summary

Introduction: Fesoterodine extended-release (ER) is an antimuscarinic agent labeled for treatment of overactive bladder (OAB). Overactive bladder is characterized by symptoms of urgency and is usually associated with urinary frequency and nocturia; approximately one-third of patients also experience incontinence. Antimuscarinic agents are the mainstay of pharmacologic therapy for OAB. These agents differ in their selectivity for the various subtypes of muscarinic receptors, leading to differences in efficacy and adverse event profiles.

Pharmacology: The presumed mechanism of action of antimuscarinic agents in OAB is the inhibition of muscarinic receptors on bladder smooth muscle, as well as on other bladder tissue.

Pharmacokinetics: Fesoterodine, an inactive pro-drug, is well-absorbed after oral administration and is rapidly hydrolyzed to the active metabolite by non-specific esterases. Plasma concentrations of the active metabolite peak at approximately 5 hours after the oral dose. The active metabolite is approximately 50% protein bound, and is converted to inactive metabolites via CYP2D6 and CYP3A4. The active metabolite of fesoterodine has an elimination half-life of approximately 7 hours. Active and inactive metabolites are excreted in the urine and in feces.

Clinical Efficacy: In 2 randomized, placebo-controlled, 12-week clinical trials, fesoterodine ER was more efficacious than placebo in treating OAB. One of the trials included tolterodine ER 4 mg as an active-control; statistical comparisons were not performed between active groups. More patients responded to fesoterodine ER 4 mg (64-75%), fesoterodine ER 8 mg (74-79%), and tolterodine ER 4 mg (72%) than to placebo (45-53%, $p < 0.001$). Micturition frequency per 24 hours was decreased more with fesoterodine (1.61-2.09) and tolterodine (1.73) than with placebo (0.95-1.08, $p < 0.05$). There was also a greater reduction in the number of urgency urinary incontinence (UUI) episodes per 24 hours with fesoterodine (1.65-2.28) and tolterodine (1.74) than with placebo (0.96-1.14, $p < 0.01$). A pooled analysis of the trials demonstrated a dose-response relationship between fesoterodine 4 mg and 8 mg doses. Response was evident as early as 2 weeks after start of therapy. A post-hoc analysis of one trial reported fesoterodine ER 8 mg was more efficacious than tolterodine ER 4 mg in 1 of 3 primary efficacy measures (percent reduction in UUI episodes per 24 hours). In two primary endpoints (treatment response and voiding frequency per 24 hours) there was no statistical difference between fesoterodine and tolterodine.

Adverse Drug Reactions/ Drug Interactions: The most common adverse events are dose-related dry mouth (19-35%) and constipation (4-6%). Risk of dry mouth, constipation, urinary retention, reduced sweating, and blurred vision, as well as central effects are increased when 2 or more antimuscarinic drugs are used concomitantly due to additive anticholinergic effects. Plasma concentrations of the active metabolite of fesoterodine may be increased by CYP3A4 inhibitors and decreased by CYP3A4 inducers.

Dosage and Administration: Initiate fesoterodine ER at 4 mg orally once daily administered without regard to meals. The dose may be increased up to 8 mg once daily based on clinical

response and tolerability. Do not exceed 4 mg daily in severe renal impairment or when used with potent CYP3A4 inhibitors. Do not use in severe hepatic impairment.

Summary: Fesoterodine ER is an antimuscarinic agent labeled for treatment of overactive bladder. Adverse effects are similar to other antimuscarinic agents. No prospective trials are available directly comparing fesoterodine to other OAB agents.

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Introduction

Fesoterodine fumarate extended-release is an antimuscarinic agent labeled for treatment of overactive bladder (OAB) with associated symptoms of urgency, frequency, and urge urinary incontinence (UUI). Fesoterodine is a prodrug which is rapidly converted to the active metabolite, 5-hydroxymethyl tolterodine.¹ Other antimuscarinic agents labeled for treatment of OAB include darifenacin, oxybutynin, solifenacin, tolterodine, and trospium.¹⁻⁹

Disease Overview

Overactive bladder is characterized by symptoms of urgency (sudden, strong desire to urinate) usually with associated urinary frequency (urinating 8 or more times per 24 hours) and nocturia (urinating two or more times nightly).^{10, 11} Approximately one-third of patients with OAB experience incontinence as well.¹¹ There are many types of urinary incontinence (eg, urge, stress, mixed, and overflow).¹² Urge and mixed incontinence are the categories that are associated with OAB.¹¹ A 2003 survey estimated the prevalence of OAB at 16.6%, impacting approximately 33 million people in the US. In the year 2000, the estimated yearly cost of OAB in the US was 12.6 billion dollars.¹³

The precise cause of overactive bladder is unknown. Sixty-four percent of patients with OAB have detrusor overactivity.¹⁴ Involuntary contractions of the detrusor muscle cause feelings of urgency and urge incontinence. Acetylcholine is the neurotransmitter primarily responsible for bladder contraction through interaction with muscarinic receptors on the detrusor muscle.¹⁰

Current nonpharmacologic treatment options for OAB include education, adjustments in fluid intake and timing, pelvic floor exercises, and biofeedback techniques.^{10, 11, 15} Pharmacologic management may benefit many patients with OAB, and may be combined with nonpharmacologic measures.^{11, 16} Antimuscarinic agents are the mainstay of pharmacologic therapy for OAB.¹⁰ These agents differ in their selectivity for the various subtypes of muscarinic receptors, leading to differences in efficacy and adverse event profiles.¹⁴ Treatment guidelines recommending specific pharmacologic therapies for OAB are not published. Table 1 presents a summary of antimuscarinic agents labeled for use in OAB. Table 2 presents a summary of selected agents which are used in the treatment of UUI and urinary frequency.

Various tools for measuring treatment efficacy and health related quality of life have been used in OAB studies. Outcome measures used to assess treatment efficacy during fesoterodine trials are summarized in Table 3.

Table 1. Comparison of Anticholinergic Agents Labeled for the Treatment of OAB^{1-9, 17-19}

Property	Darifenacin extended-release	Fesoterodine extended-release	Oxybutynin extended-release	Oxybutynin transdermal system	Solifenacin	Tolterodine immediate-release	Tolterodine extended-release	Trospium	Trospium extended-release
Trade Name	Enablex	Toviaz	Ditropan XL	Oxytrol	Vesicare	Detrol	Detrol LA	Sanctura	Sanctura XR
Generic Available?	No	No	Yes	No	No	No	No	No	No
Dosage Forms Available	Tablets: 7.5 and 15 mg	Tablets: 4 and 8 mg	Tablets: 5, 10, and 15 mg	Patch: 39 cm ² system (delivers 3.9 mg oxybutynin/day)	Tablets: 5 and 10 mg	Tablets: 1 and 2 mg	Capsules: 2 and 4 mg	Tablets: 20 mg	Capsule: 60 mg
Labeled Uses, Adults	Overactive bladder	Overactive bladder	Overactive bladder	Overactive bladder	Overactive bladder	Overactive bladder	Overactive bladder	Overactive bladder	Overactive bladder
Labeled Uses, Children	None.	None	Children \geq 6 years old: detrusor overactivity associated with a neurologic condition.	None	None	None	None	None	None
Active Parent Compound?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Active Metabolites	Negligible	5-hydroxymethyl tolterodine	N-desethyloxybutynin		Negligible	5-hydroxymethyl tolterodine		None	
Elimination Half-life	13 – 19 hours	7 hours	12 – 13 hours	7 – 8 hours	45 – 68 hours	2 – 3 hours (6.5 hours in poor metabolizers)	7 – 8 hours (18 hours in poor metabolizers)	20 hours	35 hours
Route of Elimination	Hepatic metabolism (CYP2D6 and CYP3A4)	Hepatic metabolism of active metabolite (CYP2D6 and CYP3A4)	Hepatic metabolism (CYP3A4)		Hepatic metabolism (CYP3A4)	Hepatic metabolism of tolterodine and active metabolite (CYP2D6 and CYP3A4)		Not fully defined (no CYP450 involvement)	
Labeled Adult Dosage Range	7.5 – 15 mg once daily	4 – 8 mg once daily	5 – 30 mg once daily	1 patch (3.9 mg/day system) twice weekly	5 – 10 mg once daily.	1 – 2 mg twice daily	2 – 4 mg once daily	20 mg twice daily	60 mg once daily
Comments	Administer without regard to food. Swallow whole.	Administer without regard to food. Swallow whole.	Administer without regard to food. Swallow whole.	Apply to skin on abdomen, hip, or buttock every 3 – 4 days (twice weekly). Do not reapply to the same site within 7 days.	Administer without regard to food. Swallow whole.	Administer without regard to food.	Administer without regard to food. Swallow whole.	Administer at least 1 hour prior to food or on an empty stomach.	Administer each morning on an empty stomach, at least 1 hour prior to eating.

Table 2. Comparison of Other Agents Used in the Treatment of Urinary Urge Incontinence and Urinary Frequency¹⁷⁻²³

Property	Flavoxate	Hyoscyamine sulfate immediate-release	Hyoscyamine sulfate extended-release	Oxybutynin immediate-release
Trade Name	Urispas	Levsin, Levsin SL, Symax SL, Symax Fastabs	Levbid, Symax Duotab, Symax SR	Ditropan
Generic Available?	Yes	Yes	Yes	Yes
Dosage Forms Available	Tablets: 100 mg	Sublingual tablets: 0.125 mg Orally-disintegrating tablets: 0.125 mg Tablets: 0.125, 0.15 mg	Tablets: 0.375 mg Capsules: 0.375 mg	Tablets: 5 mg Syrup: 5 mg/5 mL
Labeled Genitourinary Uses, Adults	Relieve symptoms of dysuria, urgency, nocturia, suprapubic pain, frequency, and incontinence.	Relieve symptoms of spastic bladder, neurogenic bladder, cystitis, and renal colic.		Relieve symptoms of bladder instability.
Labeled Genitourinary Uses, Children	Children ≥ 12 years old: Relieves symptoms of dysuria, urgency, nocturia, suprapubic pain, frequency, and incontinence.	Relieve symptoms of spastic bladder, neurogenic bladder, cystitis, and renal colic.		Children > 5 years old: Relieve symptoms of bladder instability.
Pharmacologic Class	Urinary antispasmodic agent	Anticholinergic agent		Anticholinergic agent
Active Metabolites	Unknown	None	None	N-desethyloxybutynin
Elimination Half-life	Unknown	2 – 3.5 hours	6.2 – 7.5 hours	2 – 3 hours
Route of Elimination	Eliminated in urine	Primarily excreted unchanged in urine		Hepatic metabolism (CYP3A4)
Labeled Adult Dosage Range	100 – 200 mg given 3 to 4 times daily	0.125 – 0.25 mg given orally or sublingually 3 – 6 times daily	0.375 – 0.75 mg given orally every 8 – 12 hours	5 mg given 2 to 4 times daily
Comments	Administer on an empty stomach	Hyoscyamine sulfate is an unapproved drug and may be in short supply. Administer without regard to food.	Hyoscyamine sulfate is an unapproved drug and may be in short supply. Administer without regard to food. Swallow whole.	Administer on an empty stomach if possible. May be administered with food if stomach upset occurs.

Table 3. Outcome Measures Used in Fesoterodine Clinical Trials²⁴⁻²⁶

Outcome Measure	Scale Used
Four-point treatment benefit scale	Affect of drug treatment on bladder symptoms. 1 = greatly improved 2 = improved 3 = no change 4 = worsened Numerical response converted to yes or no response. 1 or 2 = yes (response) 3 or 4 = no (no response)
Severity of urinary urgency	4-point scale 1 = no urgency 2 = mild urgency; could have postponed voiding for as long as necessary 3 = moderate urgency; could have postponed voiding for a short time 4 = severe urgency; must rush to bathroom to avoid wetting myself
Severity of bladder- related problems (6-point Likert Scale)	6-point scale Range: 0 (no bladder-related problems) to 5 (very severe problems). ≥2 point decrease in score indicates significant improvement.
King's Health Questionnaire (KHQ)	Total score range: 0 best to 100 (worst). 33-item assessment in 9 domains: severity/coping, emotions, sleep, personal relationships, impact of incontinence, general health, role limitations, social limitations, and physical limitations. ≥5 point change considered meaningful change for patient.
International Consultation on Incontinence Questionnaire- Short Form (ICIQ-SF)	Assesses impact of urinary problems (leakage, frequency) on daily life. 0 = low bother 21 = maximum bother

Pharmacology

Fesoterodine, an inactive pro-drug, is rapidly converted to the active metabolite 5-hydroxymethyltolterodine (5-HMT) by non-specific esterases.¹ Tolterodine is metabolized to the same active metabolite however it is converted via CYP2D6.^{7, 8} Tolterodine differs from fesoterodine in that the parent compound is active and contributes to the action of the drug.^{1, 7, 8}

The presumed mechanism of action of antimuscarinic agents in OAB is the inhibition of muscarinic receptors on bladder smooth muscle, as well as on other bladder tissue.^{27, 28} Although all five subtypes of muscarinic receptors (M₁ – M₅) have been identified in bladder tissue, M₂ and M₃ are most abundant. In the detrusor muscle, M₂ outnumbers M₃ in a ratio of 3:1.²⁷ The M₃ receptor is considered most important in detrusor contraction. The M₂ receptor may contribute to contraction by inhibiting relaxation of bladder smooth muscle, among other possible mechanisms.^{14, 29} The roles the various muscarinic receptors play in bladder activity is still not fully known, and it is not yet known whether muscarinic receptor selectivity (M₃) offers a therapeutic advantage.²⁷ Antimuscarinic agents used to treat OAB vary in their affinities for the various subtypes of muscarinic receptors. In vitro and animal studies indicate that fesoterodine and its active metabolite are non-selective in affinity for the muscarinic receptor subtypes.^{29, 30} The affinity of medications for these receptors influences the efficacy and adverse effect profiles observed. Muscarinic M₃ receptors are involved in the regulation of salivation, intestinal smooth muscle contraction, and pupillary constriction.¹⁴ The most commonly reported adverse events associated with muscarinic inhibitors include dry mouth, constipation, and blurred vision.¹⁴

Pharmacokinetics

Fesoterodine is well-absorbed after oral administration.¹ Non-specific esterases rapidly hydrolyze fesoterodine to its active metabolite, 5-HMT, such that the parent compound is not detectable in plasma. Approximately 52% of the dose is bioavailable as the active metabolite. Plasma concentrations peak at approximately 5 hours after the oral dose, and are dose-proportional. Multiple dosing does not produce 5-HMT accumulation in plasma. Food does not significantly alter the pharmacokinetics of fesoterodine ER. The volume of distribution of 5-HMT is 169 L; 5-HMT is approximately 50% protein bound. The active metabolite is converted to inactive metabolites via CYP2D6 and CYP3A4 isoenzymes. Higher plasma concentrations of 5-HMT are reported in individuals who are poor CYP2D6 metabolizers compared with extensive metabolizers; peak plasma concentrations are 1.7 times higher and total drug exposure (area under the curve) is two times higher. The active metabolite of fesoterodine has an elimination half-life of approximately 7 hours after oral administration of fesoterodine ER. It is excreted as metabolites in the urine, both active (16%) and inactive (53%), and in the feces (7%).¹

Special Populations

The pharmacokinetics of fesoterodine are not significantly affected by age or gender.¹ Fesoterodine has not been studied in children. No differences in pharmacokinetics have been reported between healthy Black and Caucasian subjects.¹

In patients with mild to moderate renal insufficiency, peak plasma concentrations may be elevated up to 1.5 times normal and area under the curve up to 1.8 times normal, however, no dosage adjustment is required.¹ In severe renal insufficiency (creatinine clearance <30 mL/min), peak plasma concentrations may be doubled and the area under the curve 2.3 times normal. Do not exceed a daily fesoterodine dose of 4 mg in patients with severe renal insufficiency.¹

Elimination of the active metabolite is reduced in hepatic dysfunction.¹ In patients with moderate hepatic impairment, elevations in peak plasma concentration (1.4 times normal) and area under the curve (2.1 times normal) have been reported. Dosage adjustment is not recommended in patients with mild to moderate hepatic impairment. Do not use fesoterodine in patients with severe hepatic impairment (Child-Pugh C).¹

Clinical Efficacy

Fesoterodine has not been directly compared to other antimuscarinic agents in prospective clinical trials. In 2 randomized, placebo-controlled, 12-week clinical trials,^{26, 31} fesoterodine ER 4 mg and 8 mg per day were more efficacious than placebo in treating OAB. More patients responded to fesoterodine ER 4 mg (64-75%) and to fesoterodine ER 8 mg (74-79%) than to placebo (45-53%, $p < 0.001$). The reduction in mean number of micturitions per 24 hours was greater for fesoterodine groups (1.61 – 2.09) than for placebo (0.95 – 1.08, $p < 0.05$). Also, there was a greater reduction in the number of UII episodes per 24 hours in fesoterodine groups (1.65 – 2.28) than in placebo groups (0.96 – 1.14, $p < 0.01$). One of the trials³¹ included tolterodine extended-release (ER) 4 mg as an active control group. Both fesoterodine ER and tolterodine ER were superior to placebo in all primary endpoints. Statistical comparisons were

not reported between tolterodine and fesoterodine groups in the original trial analysis. Chapple et al published a post-hoc analysis of an earlier prospective trial³¹ comparing the maximum daily dose of fesoterodine ER (8 mg) with the maximum daily dose of tolterodine ER (4 mg).²⁴ There was no statistical difference between fesoterodine and tolterodine in two of the three primary endpoints (voiding frequency and rate of positive response). The third primary endpoint, mean percent reduction in incontinence episodes per 24 hours, was greater with fesoterodine (88%) than with tolterodine (70%) or placebo (50%; $p < 0.001$ fesoterodine vs tolterodine and placebo). The two clinical trials are summarized in Table 4.

Similar protocols and criteria were used in the two clinical trials.^{26, 31} Adults with OAB symptoms of at least moderate intensity and at least 6 month duration were included. Subjects were randomized to study groups if the following criteria were met: urinary frequency (≥ 8 voids/24 hours) and urgency (≥ 6 episodes per 24 hours) or UUI (≥ 3 episodes per 24 hours). Inclusion criteria were amended in both studies to require UUI symptoms in order to assure at least 80% of subjects in each group had incontinence at baseline by this measure. Patients recorded micturition times, incontinence episode times, and times and severity of urgency episodes in 3-day diaries at weeks 2, 8, and 12 of therapy.

Two pooled analyses of the two prospective fesoterodine clinical trials have been published,^{25, 32} one comparing efficacy of fesoterodine ER 4 mg to fesoterodine ER 8 mg,³² the other comparing the impact on quality of life measures.²⁵ Khullar et al³² compared fesoterodine ER 4 mg (n=554), fesoterodine ER 8 mg (n=566), and placebo (n=554). A positive, sustained treatment response was noted in both fesoterodine groups as early as 2 weeks after treatment began ($p < 0.05$ vs placebo). Fesoterodine ER 8 mg was more effective than fesoterodine ER 4 mg in the following measures ($p < 0.05$): positive treatment response (77% vs 69%), mean reduction in UUI episodes per 24 hours (2.3 vs 1.9), change (improvement) in mean volume voided (33.6 mL vs 22.2 mL), and continent days per week (3.1 vs 2.6). Fesoterodine ER 8 mg did not perform better than fesoterodine ER 4 mg in two measures: micturition frequency per 24 hours and number of urgency episodes per 24 hours. Both fesoterodine doses were significantly more effective than placebo in all evaluated measures ($p < 0.05$).³²

Kelleher et al²⁵ evaluated the quality of life measures reported in the two clinical trials. By week 12, all active treatment groups reported statistically and clinically meaningful improvements in at least seven of the nine domains on the King's Health Questionnaire ($p < 0.01$ active groups vs placebo). In two domains, fesoterodine ER 8 mg performed better than fesoterodine ER 4 mg ($p < 0.05$); there were no statistical differences between fesoterodine ER 8 mg and tolterodine ER 4 mg. All active treatment groups were significantly better than placebo on the International Consultation on Incontinence Questionnaire-Short Form ($p < 0.001$); there were no significant differences between active treatment groups. On a 6-point Likert scale, the rate of patients reporting major improvement in bladder condition at 12 weeks was greater in fesoterodine ER 4 mg (33%), fesoterodine ER 8 mg (38%), and tolterodine ER 4 mg (34%) than in placebo (21%, $p < 0.001$).²⁵

Special Populations

Fesoterodine has not been studied for use in children.¹ Clinical trials evaluating fesoterodine included 515 (33%) patients at least 65 years of age, 140 of whom were at least 75

years of age. There was no overall difference in efficacy or safety reported in older patients compared to patients under the age of 65. Higher rates of antimuscarinic adverse events (eg, dry mouth, constipation, and dyspepsia) were reported in patients 75 years of age and older compared to younger patients.¹

Table 4. Placebo-Controlled Efficacy Trials of Fesoterodine in Overactive Bladder

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes			Grade *
				Results	Response Rate	Discontinuation Rate and Adverse Events	
Chapple et al, 2007 ⁵¹ Experimental parallel: randomized, double-blind, double-dummy, placebo-controlled, multicenter	1135	Men and women ≥18 years of age who have OAB with urinary urgency ≥6 months, ≥8 micturitions/24 hours, and ≥6 urgency episodes or ≥3 UI episodes/24 hours. OAB must cause ≥ moderate problems. Mean age: 57 years; 80% were women; mean duration of OAB symptoms: 8-9 years Exclusion criteria: Significant lower urinary tract pathology, recurrent urinary tract infections, postvoid residual volume >100 mL, neurological disease related to bladder symptoms, cardiac rate or rhythm abnormalities, antimuscarinic therapy within 2 weeks of screening, electrostimulation for bladder training within 4 weeks of study.	Study drugs administered orally once daily in the morning. Fesoterodine ER 4 mg n = 272 Fesoterodine ER 8 mg n = 288 Tolterodine ER 4 mg n = 290 Placebo n = 285 Treatment duration: 12 weeks At baseline, and prior to study visits at weeks 2, 8, and 12, patients recorded micturition times, incontinence episodes, and severity of urgency episodes in 3-day diaries. Voided volumes were also recorded for 1 of the 3 days. Treatment benefit assessed on patient-reported 4-point scale.	Fesoterodine >placebo Tolterodine >placebo	Primary endpoints: Mean number micturitions/24 hour period; change from baseline at week 12 <ul style="list-style-type: none"> Fesoterodine ER 4 mg -1.76 ± 0.17 Fesoterodine ER 8 mg -1.88 ± 0.16 Tolterodine ER 4 mg -1.73 ± 0.16 Placebo -0.95 ± 0.16 $p \leq 0.001$ all active groups vs placebo UI episodes/24 hours, mean change from baseline at week 12 <ul style="list-style-type: none"> Fesoterodine ER 4 mg -1.95 ± 0.17 Fesoterodine ER 8 mg -2.22 ± 0.16 Tolterodine ER 4 mg -1.74 ± 0.16 Placebo -1.14 ± 0.16 $p < 0.01$ all active groups vs placebo Rate of positive treatment response on patient-rated, 4-point scale at week 12 <ul style="list-style-type: none"> Fesoterodine ER 4 mg 75% Fesoterodine ER 8 mg 79% Tolterodine ER 4 mg 72% Placebo 53% $p < 0.001$ all active groups vs placebo Secondary endpoints, change from baseline at 12 weeks: Mean volume voided/micturition, daytime micturitions/24 hours, and number of urgency episodes/24 hours <ul style="list-style-type: none"> all active groups > placebo ($p < 0.01$) Number of continent days/week <ul style="list-style-type: none"> Fesoterodine > placebo ($p < 0.01$) Tolterodine NS vs placebo Nocturnal micturitions/24 hours <ul style="list-style-type: none"> No active group was better than placebo 	Overall discontinuation rates <ul style="list-style-type: none"> Fesoterodine ER 4 mg 41/272 (15%) Fesoterodine ER 8 mg 36/288 (13%) Tolterodine ER 4 mg 37/290 (13%) Placebo 33/285 (12%) Discontinuation due to adverse events <ul style="list-style-type: none"> Fesoterodine ER 4 mg 7/272 (3%) Fesoterodine ER 8 mg 14/287 (5%) Tolterodine ER 4 mg 9/290 (3%) Placebo 6/283 (2%) Adverse events: <u>Dry mouth</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg 22% Fesoterodine ER 8 mg 34% Tolterodine ER 4 mg 17% Placebo 7% <u>Constipation</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg 3.3% Fesoterodine ER 8 mg 4.5% Tolterodine ER 4 mg 2.8% Placebo 1.4% 	1

Abbreviations: N or n = number of patients enrolled in trial or specific treatment group; NS = not statistically significant; OAB = overactive bladder; UI = urgency urinary incontinence.

* Grade of Scientific Evidence. Refer to Appendix for definitions.

Table 4, continued. Placebo-Controlled Efficacy Trials of Fesoterodine in Overactive Bladder

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes			Grade *
				Results	Response Rate	Discontinuation Rate and Adverse Events	
Nitti et al, 2007 ²⁶ Experimental parallel: randomized, double-blind, placebo-controlled, multicenter	836	Men and women ≥18 years of age who have OAB with urinary urgency ≥6 months, ≥8 micturitions/24 hours, and ≥6 urgency episodes or ≥3 UUI episodes/24 hours. OAB must cause ≥ moderate problems. Mean age: 59 years (range 21 – 91); 76% were women; mean duration of OAB symptoms: 10 years Exclusion criteria: Significant lower urinary tract pathology, recurrent urinary tract infections, post void residual volume >100 mL, neurogenic cause of bladder symptoms, cardiac arrhythmias, current antimuscarinic therapy, electrostimulation or bladder training within 4 weeks of study.	Study drugs administered orally once daily in the morning. Fesoterodine ER 4 mg n = 283 Fesoterodine ER 8 mg n = 279 Placebo n = 274 Treatment duration: 12 weeks At baseline, and prior to study visits at weeks 2, 8, and 12, patients recorded micturition times, incontinence episodes, and severity of urgency episodes in 3-day diaries. Voided volumes were also recorded for 1 of the 3 days. Treatment benefit assessed on patient-reported 4-point scale.	Fesoterodine > placebo	Primary endpoints: <u>Mean number micturitions/24 hour period; change from baseline at week 12</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg -1.61 ± 0.18 Fesoterodine ER 8 mg -2.09 ± 0.18 Placebo -1.08 ± 0.18 <p>p<0.05 active groups vs placebo</p> <u>UUI episodes/24 hours, mean change from baseline at week 12</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg -1.65 ± 0.16 Fesoterodine ER 8 mg -2.28 ± 0.16 Placebo -0.96 ± 0.17 <p>p<0.01 active groups vs placebo</p> <u>Rate of positive treatment response on patient-rated, 4-point scale at week 12</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg 64% Fesoterodine ER 8 mg 74% Placebo 45% <p>p<0.001 active groups vs placebo</p> Secondary endpoints, change from baseline at 12 weeks: <u>number of urgency episodes/24 hours and number of continent days/week</u> <ul style="list-style-type: none"> active groups > placebo (p<0.001) <u>Mean volume voided/micturition and daytime micturitions/24 hours</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg (NS vs placebo) Fesoterodine ER 8 mg > placebo (p<0.001) • <u>Nocturnal micturitions/24 hours</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg > placebo (p<0.05) Fesoterodine ER 8 mg (NS vs placebo) 	Overall discontinuation rates <ul style="list-style-type: none"> Fesoterodine ER 4 mg 58/283 (20%) Fesoterodine ER 8 mg 56/279 (20%) Placebo 41/274 (15%) Discontinuation due to adverse events <ul style="list-style-type: none"> Fesoterodine ER 4 mg 17/282 (6%) Fesoterodine ER 8 mg 25/279 (9%) Placebo 11/271 (4%) Adverse events: <u>Dry mouth</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg 16% Fesoterodine ER 8 mg 36% Placebo 7% <u>Constipation</u> <ul style="list-style-type: none"> Fesoterodine ER 4 mg 5% Fesoterodine ER 8 mg 8% Placebo 3% 	1

Abbreviations: N or n = number of patients enrolled in trial or specific treatment group; NS = not statistically significant; OAB = overactive bladder; UUI = urgency urinary incontinence.

* Grade of Scientific Evidence. Refer to Appendix for definitions.

Adverse Drug Reactions

The most common adverse event reported in clinical trials in fesoterodine groups was dry mouth.¹ This occurred more frequently with 8 mg daily (35%) than with 4 mg daily (19%). Discontinuation rates due to dry mouth were 0.4% (4 mg dose), 0.8% (8 mg dose), and 0.4% (placebo). Another commonly reported adverse event was constipation which occurred at rates of 4% (fesoterodine ER 4 mg), 6% (fesoterodine ER 8 mg) and 2% (placebo). Most occurrences of constipation and dry mouth were mild to moderate in severity. Serious adverse events reported during placebo-controlled trials included 1 case each of angina, chest pain, gastroenteritis, and QT prolongation. During open-label trials serious adverse events included urinary retention, diverticulitis, constipation, irritable bowel syndrome, and QT prolongation.¹ Table 5 lists adverse events reported during OAB clinical trials of the various antimuscarinic agents as reported in product labeling. It is difficult to make comparisons between the agents with regard to adverse reactions because the product labeling for each agent reports the information differently.

Contraindications and Black Box Warnings

Patients who have urinary or gastric retention should not use fesoterodine.¹ Fesoterodine is also contraindicated in patients who have uncontrolled narrow-angle glaucoma. Fesoterodine product labeling contains no black box warnings.¹

Table 5. Adverse Event Rates Reported for Antimuscarinic Agents During OAB Studies as Reported in Product Labeling¹⁻⁹

Agent	Darifenacin Extended-Release	Fesoterodine Extended-Release	Oxybutynin Extended-Release	Oxybutynin Transdermal ^a	Solifenacin	Tolterodine Immediate-Release	Tolterodine Extended-Release	Trospium	Trospium Extended-Release
Dose	7.5-15mg/day	4 - 8 mg/day	5-30mg/day	3.9 mg/day	5-10mg/day	2 mg bid	4 mg /day	20 mg bid	60 mg/day
Reporting parameters	Percent AE occurring in $\geq 2\%$ and more often than placebo ^b n= 671	Percent AE occurring in $\geq 1\%$ and more often than placebo ^b n=1120	Percent AE occurring in $\geq 5\%$ and in post-marketing studies ^b n=1005	Percent AE occurring in $\geq 2\%$ and more often than placebo ^b n=246	Percent AE occurring in $\geq 1\%$ and more often than placebo ^b n=1811	Percent AE occurring in $\geq 1\%$ and more often than placebo ^b n=986	Percent AE occurring in $\geq 1\%$ and more often than placebo ^b n=505	Percent AE occurring in $\geq 1\%$ and more often than placebo ^c n=591	Percent AE occurring in $\geq 1\%$ ^c or $\geq 2\%$ and more often than placebo ^b n=578
Gastrointestinal									
dry mouth	20-35	19-35	29-61	4-10	11-28	35	23	20	11
constipation	15-21	4-6	7-13	3	5-13	7	6	10	9
dyspepsia	3-8	2	5-7	--	1-4	4	3	1	1
nausea	2-3	<1-2	2-9	--	2-3	--	--	--	1
abdominal pain	2-4	<1-1	--	--	1-2	5	4	2	1
diarrhea	<1-2	--	7-9	3	--	4	--	--	--
flatulence	--	--	--	--	--	--	--	1	2
abdominal distention	--	--	--	--	--	--	--	--	1
vomiting	--	--	--	--	<1-1	--	--	--	--
Urogenital									
urinary tract infection	5	3-4	5	--	3-5	--	--	--	1-7
dysuria	--	1-2	--	2	--	2	1	--	--
urinary retention	--	1	--	--	0-1	--	--	1	--
Nervous System									
insomnia	--	<1-1	--	--	--	--	--	--	--
dizziness or vertigo	<1-2	--	4-6	--	2	5	2	--	--
somnolence	--	--	2-12	--	--	3	3	--	--
headache	--		6-10	--	--	7	6	4	--
Eye									
dry eyes	2	1-4	3-6	--	<1-2	3	3	1	2
vision changes	--	--	1-8	2	4-5	2	1	--	--

Abbreviation: AE = adverse events.

^a application site reactions were the most frequently reported adverse event with transdermal oxybutynin. These reactions included burning ($>1\%$), erythema (5.6% – 8.3%), macules (2.5%), pruritus (14% – 16.8%), rash (3.3%), and vesicles (3.2%). ^b reported regardless of causality. ^c reported if judged possibly related to study drug.

Table 5, cont. Adverse Event Rates Reported for Antimuscarinic Agents in OAB Studies as Reported in Product Labeling¹⁻⁹

Agent	Darifenacin Extended-Release	Fesoterodine Extended-Release	Oxybutynin Extended-Release	Oxybutynin Transdermal ^a	Solifenacin	Tolterodine Immediate-Release	Tolterodine Extended-Release	Trospium	Trospium Extended-Release
Dose	7.5-15mg/day	4 - 8 mg/day	5-30mg/day	3.9 mg/day	5-10mg/day	2 mg bid	4 mg /day	20 mg bid	60 mg/day
Reporting parameters	Percent AE occurring in $\geq 2\%$ and more often than placebo ^b n= 671	Percent AE occurring in $\geq 1\%$ and more often than placebo ^b n=1120	Percent AE occurring in $\geq 5\%$ and in post-marketing studies ^b n=1005	Percent AE occurring in $\geq 2\%$ and more often than placebo ^b n=246	Percent AE occurring in $\geq 1\%$ and more often than placebo ^b n=1811	Percent AE occurring in $\geq 1\%$ and more often than placebo ^b n=986	Percent AE occurring in $\geq 1\%$ and more often than placebo ^b n=505	Percent AE occurring in $\geq 1\%$ and more often than placebo ^c n=591	Percent AE occurring in $\geq 1\%$ ^c or $\geq 2\%$ and more often than placebo ^b n=578
Respiratory									
upper respiratory tract infection	--	2-3	--	--	--	--	--	--	--
cough	--	<1-2	--	--	<1-1	--	--	--	--
dry throat	--	<1-2	--	--	--	--	--	--	--
nasal dryness	--	--	--	--	--	--	--	--	1
nasopharyngitis	--	--	--	--	--	--	--	--	3
pharyngitis	--	--	--	--	<1-1	--	--	--	--
rhinitis	--	--	2-6	--	--	--	--	--	--
sinusitis	--	--	--	--	--	--	2	--	--
Body As A Whole									
back pain	--	<1-2	--	--	--	--	--	--	--
rash	--	<1-1	--	--	--	--	--	--	--
edema, peripheral	--	<1-1	--	--	--	--	--	--	--
edema, lower limb	--	--	--	--	<1-1	--	--	--	--
asthenia or fatigue	2-3	--	3-7	--	1-2	4	2	2	--
anxiety	--	--	--	--	--	--	1	--	--
pain	--	--	4-7	--	--	--	--	--	--
arthralgia	--	--	--	--	--	2	--	--	--
influenza	--	--	--	--	<1-2	--	--	--	2
flu-like symptoms	--	--	--	--	--	3	--	--	--
depression	--	--	--	--	<1-1	--	--	--	--
hypertension	--	--	--	--	<1-1	--	--	--	--
chest pain	--	--	--	--	--	2	--	--	--
dry skin	--	--	--	--	--	1	--	--	--
weight gain	--	--	--	--	--	1	--	--	--
infection	--	--	--	--	--	1	--	--	--

Abbreviation: AE = adverse events.

^a application site reactions were the most frequently reported adverse event with transdermal oxybutynin. These reactions included burning ($>1\%$), erythema (5.6% – 8.3%), macules (2.5%), pruritus (14% – 16.8%), rash (3.3%), and vesicles (3.2%). ^b reported regardless of causality. ^c reported if judged possibly related to study drug.

Drug Interactions

Both pharmacokinetic and pharmacodynamic drug interactions may occur with fesoterodine. In vitro experiments demonstrate 5-HMT does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 nor induce 1A2, 2B6, 2C9, 2C19, or 3A4.¹ Table 6 summarizes reported and potential drug-drug interactions with fesoterodine.

Table 6. Reported and Potential Drug-Drug Interactions with Fesoterodine^{1,33}

Interacting Medication	Interaction	Recommendation
CYP3A4 inhibitors, potent (eg, ketoconazole, itraconazole and clarithromycin)	Increased plasma concentrations of fesoterodine active metabolite Ketoconazole 200 mg twice daily x 5 days increased peak plasma concentrations of fesoterodine active metabolite. Increases occurred in both poor and extensive CYP2D6 metabolizers.	Do not exceed 4 mg daily dose of fesoterodine in patients taking potent CYP3A4 inhibitors.
CYP3A4 inhibitors, weak or moderate (eg, erythromycin)	possible increase in fesoterodine plasma concentrations	Assess response and tolerability of fesoterodine 4 mg dose before increasing to 8 mg dose in patients taking weak or moderate CYP3A4 inhibitors.
CYP3A4 inducers (eg, rifampin)	Reduced plasma concentrations of fesoterodine active metabolite. Rifampin 600 mg daily decreased peak plasma concentrations of fesoterodine active metabolite by approximately 70% after fesoterodine ER 8 mg dose.	No fesoterodine dosing adjustments are recommended. Monitor for efficacy.
CYP2D6 inhibitors	Not tested clinically.	No fesoterodine dosing adjustments are recommended.
Agents with anticholinergic properties (eg, tricyclic antidepressants, antiemetics, sedating antihistamines, antispasmodics, certain antipsychotics and muscle relaxants)	Additive anticholinergic effects. Increased frequency and severity adverse events such as dry mouth, constipation, urinary retention, reduced sweating, and blurred vision, as well as central effects such as confusion, aggressive behavior, or memory problems may occur when 2 or more antimuscarinic drugs are use concomitantly.	Use with caution and monitor for anticholinergic adverse effects.
Alcohol	increased drowsiness	Counsel patients regarding this potential interaction.

Dosage and Administration

The initial recommended dose is fesoterodine ER 4 mg once daily.¹ The daily dose may be increased to 8 mg based on clinical response and tolerability. Fesoterodine ER tablets should be swallowed whole, and may be administered without regard to food. Do not divide, chew, or crush the tablets.¹

Do not exceed the 4 mg daily dose in patients with severe renal impairment or in patients who are taking potent CYP3A4 inhibitors.¹ Do not use fesoterodine in patients who have severe

hepatic impairment, uncontrolled narrow-angle glaucoma, or in patients with urinary or gastric retention. Use with caution in patients who have decreased gastrointestinal motility, controlled narrow-angle glaucoma, bladder outlet obstruction, or in patients with myasthenia gravis.¹

Fesoterodine is available as 4 mg and 8 mg extended-release tablets. Store at room temperature and protect from moisture.¹

Monitoring

Monitor patients for excessive anticholinergic effects such as constipation, urinary retention, blurred vision, and drowsiness. Inform patients of the signs of heat prostration when fesoterodine is used in hot environments, as antimuscarinic agents may cause decreased sweating.¹

Critical Issues

- Fesoterodine ER is more effective than placebo for treatment of OAB.
- No prospective trials have compared fesoterodine ER with other agents for OAB.
- A post-hoc analysis of one trial reported fesoterodine ER 8 mg was more efficacious than tolterodine ER 4 mg in 1 of 3 primary efficacy measures (percent reduction in UUI episodes per 24 hours). In two primary endpoints (positive treatment response and percent change in voiding frequency per 24 hours) there was no statistical difference between fesoterodine and tolterodine groups.

Summary

Fesoterodine ER is an antimuscarinic agent labeled for treatment of overactive bladder. Fesoterodine, an inactive pro-drug, is well-absorbed after oral administration and is rapidly hydrolyzed to the active metabolite, 5-HMT, by non-specific esterases. Adverse effects are similar to other antimuscarinic agents. No trials are available prospectively comparing fesoterodine to other OAB agents.

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Appendix: Grades of Scientific Evidence

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| Grade 1. | Evidence from randomized, blinded, placebo-controlled, clinical trials in peer reviewed journals |
| Grade 2. | Non-randomized controlled trials |
| Grade 3. | Non-randomized historical cohort studies. Other studies with non-experimental designs (eg, population based studies, case-control studies) |
| Grade 4. | Case reports, case series, abstracts of trials |
| Grade 5. | Consensus of experts where data are incomplete or inconsistent |